Newborn Screening for X-linked Adrenoleukodystrophy (X-ALD): Final Report from the Condition Review Workgroup

Alex R. Kemper, MD, MPH, MS
August 27, 2015

Not for distribution without permission.
## Condition Review Workgroup (CRW)

<table>
<thead>
<tr>
<th>CRW Members</th>
<th>Role</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alex R. Kemper, MD, MPH, MS</td>
<td>Chair, Clinical Pediatrician, USPSTF</td>
<td>Duke University</td>
</tr>
<tr>
<td>Jeff Brosco, MD, PhD</td>
<td>Pediatric /NBS Bioethicist, and Regional Title V Services</td>
<td>Mailman Center for Child Development CMS South Region (Florida's Title V Agency) Pediatrics Bioethics Committee, Jackson Health System</td>
</tr>
<tr>
<td>Anne M. Comeau, PhD</td>
<td>State NBS Public Health Program</td>
<td>New England NBS Program, University of Mass Medical School</td>
</tr>
<tr>
<td>Nancy S. Green, MD</td>
<td>Clinical Pediatric – Hematology Specialist</td>
<td>Department of Pediatrics, Columbia University Medical Center</td>
</tr>
<tr>
<td>Scott Grosse, PhD</td>
<td>Federal Advisor, Health Economist</td>
<td>Nat’l Center on Birth Defects &amp; Developmental Disabilities, CDC</td>
</tr>
<tr>
<td>Jelili Ojodu, MPH</td>
<td>Public Health Impact Task Leader</td>
<td>NBS &amp; Genetics, Association of Public Health Laboratories</td>
</tr>
<tr>
<td>Lisa Prosser, PhD</td>
<td>Decision Analysis Leader, NBS Health Economist</td>
<td>Health Management &amp; Policy/ SPH; Pediatrics/Univ of Michigan Med School</td>
</tr>
<tr>
<td>Susan Tanksley, PhD</td>
<td>State NBS Public Health Program</td>
<td>Newborn Screening Laboratory TX Department of State Health Services</td>
</tr>
<tr>
<td>Jennifer Kwon, MD</td>
<td>Clinical Pediatric Neurologist, LT follow up</td>
<td>Clinic for Inherited Metabolic Diseases, Golisano Children's Hospital, U of Rochester</td>
</tr>
<tr>
<td>K.K. Lam, PhD</td>
<td>Project Leader</td>
<td>Duke University</td>
</tr>
<tr>
<td>Fred Lorey, PhD</td>
<td>Committee Representative for X-ALD Review</td>
<td>Genetic Disease Screening Program California Department of Public Health</td>
</tr>
<tr>
<td>Donald Bailey, PhD</td>
<td>Committee Representative for X-ALD Review</td>
<td>Early Childhood Development RTI International</td>
</tr>
</tbody>
</table>
Outline

• Highlight key findings from the systematic evidence review and supplemental data analyses

• Describe the anticipated bounds of benefit and harm

• Summarize the capability of state newborn screening programs to offer comprehensive screening for X-ALD
Overview: X-Linked Adrenoleukodystrophy (X-ALD)

- Peroxisomal disorder affecting the adrenal cortex and the central nervous system (cerebral demyelination and spinal cord/peripheral neuropathy)
- Broad phenotype spectrum ranging in presenting symptom, severity and age of onset (~1 year through adulthood)
- Male (hemizygote) X-ALD – about 90% affected with significant, multi-symptom involvement, with onset from 1 year through adulthood.
- Female (heterozygote) X-ALD – based on 46 women in the Netherlands, age range 22-76 years (average 48 years) in a referral center (Engelen et al., 2014)
  - Symptoms – 18% < 40 years; up to 88% in women by 60 years; symptoms ranged from myelopathy, peripheral neuropathy, fecal incontinence
Prevalence of X-ALD in the U.S.

<table>
<thead>
<tr>
<th>Category</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All X-ALD cases</td>
<td>1 in 16,900</td>
</tr>
<tr>
<td>Male X-ALD</td>
<td>1 in 42,000</td>
</tr>
<tr>
<td>Female X-ALD</td>
<td>1 in 28,000</td>
</tr>
</tbody>
</table>

- based on clinical referral and extended family testing of males

## Prevalence of X-ALD in Males

<table>
<thead>
<tr>
<th>Study Authors &amp; Year</th>
<th>Country/Region</th>
<th>Base Years</th>
<th>Male X-ALD Hemizygotes per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Detection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirk et al., 1998</td>
<td>Australia</td>
<td>1981 - 1996</td>
<td>1.6</td>
</tr>
<tr>
<td>Di Biase et al., 1998</td>
<td>Italy</td>
<td>1990 - 1995</td>
<td>3.6</td>
</tr>
<tr>
<td>Takemoto et al., 2002</td>
<td>Japan</td>
<td>1990 - 1999</td>
<td>2 - 3.3</td>
</tr>
<tr>
<td>Stradomska et al., 2009</td>
<td>Poland</td>
<td>1994 - 2004</td>
<td>2.9</td>
</tr>
<tr>
<td>Jardim et al., 2010</td>
<td>Brazil</td>
<td>2002 - 2007</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Clinical Detection + Extended Family Screening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# X-ALD Clinical Spectrum

<table>
<thead>
<tr>
<th></th>
<th>CHILDHOOD - Males</th>
<th>ADULT (Males)</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal Insufficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset Age (Yrs)</td>
<td>&gt;1 - 13</td>
<td>2.5–10</td>
<td>10–21</td>
</tr>
<tr>
<td>Frequency (%)</td>
<td>60-90 (~10% AI only)</td>
<td>CHILD 31 – 35</td>
<td>ADOL 4 – 7</td>
</tr>
<tr>
<td>Progression</td>
<td>–</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>–</td>
<td>Extensive</td>
<td>Some</td>
</tr>
<tr>
<td>Brain MRI - White matter lesions</td>
<td>–</td>
<td>Extensive</td>
<td>Some</td>
</tr>
<tr>
<td>Behavioral &amp; Cognitive Disorder</td>
<td>Extensive</td>
<td>Some</td>
<td>Possible</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>–</td>
<td>Rare</td>
<td>Possible</td>
</tr>
<tr>
<td>Life Expectancy (untreated)</td>
<td>Death within 3 years after onset</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cerebral ALD (CALD)** *(about 90% of C-CALD also have adrenal insufficiency)*
Genetics of X-ALD

- ABCD1 = single causative gene of X-ALD, maps to Xq28. ABCD1 gene encodes adrenoleukodystrophy protein (ALDP), which facilitates transport of very long-chain fatty acids (VLCFA) into peroxisomes. ALDP deficiency impairs VLCFA beta-oxidations, leading to elevation of VLCFA.
- >600 mutations identified (http://www.x-ald.nl); most are unique
- No genotype-phenotype correlation, even within families
X-ALD Newborn Screening

- Measurement of C26:0 lysophosphatidylcholine (26:0-lyso-PC) as marker for VLCFA in DBS
- Tandem mass spectrometry (MS/MS)
  - High Performance Liquid Chromatography (HPCL)
  - Can be multiplexed – Krabbe disease and Pompe disease (NY)
  - CDC Proficiency Tests Expected Fall 2015
- Small technical validation and pilot studies
  - Low number of positives (X-ALD, other peroxisomal disorders, false positives)
  - Expected to detect about 80-90% of heterozygote females
  - High-throughput feasibility
Establishing the X-ALD Diagnosis

• Increased Very long-chain fatty acids
  – Most important laboratory assay is VLCFA concentration in plasma

• X-ALD diagnosis – ABCD1 mutations
  – DNA diagnostic test for X-ALD involving non-nested genomic amplification of the ABDC1 gene, followed by sequencing and analysis with fluorescence
  – Because of the lack of genotype-phenotype correlation, this is not required to establish the diagnosis. However, this information can be of use to specialists and is a component of the NY newborn screening program
Establishing the X-ALD Diagnosis (cont’)

• Clinical Assessment
  – Neuroimaging - *Brain MRI / Loes severity scale – always abnormal in neurologically symptomatic males*
  – Clinical Symptoms
    • ADHD symptoms, signs of dementia, difficulties understanding spoken language, progressive disturbance in behavior, coordination, handwriting, vision, other neurological disturbances.
    • *Primary adrenocortical insufficiency co-occurs in ~90% of Cerebral X-ALD*
  – Asymptomatic
    • *May have ABCD1 mutations and elevated VLCFA but be asymptomatic and require follow-up and monitoring*
Treatment Strategies

• **Hematopoietic Stem Cell Transplantation (HSCT)**
  – Requires either matched-related donor (ideally non-heterozygote) or closely matched cord blood (overall, 95% will have cord-blood match)
  – May reduce risk or progression of neurological degeneration in early stage CALD
  – Risk of Graft-versus-Host disease depends on the match, age, prophylaxis
  – Risk of mortality for non-cancerous conditions ~5% within the first few years
  – Risk of failure to engraft (likely small)

• **Adrenal Cortisol Replacement therapy**
  – Necessary for adrenal insufficiency

• **Gene Therapy for X-ALD**
  – 2 successful case studies in France (Two 7-year-old boys, early CALD), cerebral disease progression halted after 14-16 months. Clinical trial underway.

• **Lorenzo’s Oil**

• **N-acetyl-L-cysteine**
  – Case series suggests that it can help with advanced brain involvement
Management of Presymptomatic X-ALD

- MRI is sensitive and reliable marker for disease progression
  
  **Loes Score** – MRI disease severity rating: <9 recommend for HCT

- Endocrinologist referral to monitor adrenal function
  
  Serum ACTH levels, ACTH stimulation test for used to detect early signs

Engelen et al. 2012. X-linked adrenoleukodystrophy: Clinical presentation and guidelines for diagnosis, follow-up and management. Orph J Rare Dis. 7

- **Keywords:**
  - ("Adrenoleukodystrophy"[Mesh]) OR ("Adrenoleukodystrophy"[tiab]) OR ("Adrenoleukodystrophy/therapy"[Mesh]) OR ("X-ALD"[tiab]) OR ("very long-chain fatty acids"[All Fields]) OR ("VLCFA"[tiab]) OR ("Lorenzo’s oil"[Supplementary Concept]) OR ("Lorenzo’s oil"[tiab]) AND ("humans"[Mesh] NOT "animals"[mesh]) AND Limits: English.

- **Articles through PubMed, EMBASE, & CINAHL since inception (3,157)**

- **Articles screened for title/abstract relevance (1,646)**

- **Articles assessed for initial eligibility (1,014)**

- **Screening by two independent reviewers**

**Figure 1. PRISMA Diagram of Published Literature Search**

- Records identified through database searching
  - N = 3,157

- Records screened by title and abstract
  - N = 1646

- Full-text articles assessed for eligibility
  - N = 1014

- Studies retained for extraction and review

- Removed from screen (non-human, duplicates)
  - N=1511

- Records removed
  - N = 632

- Full-text articles excluded
  - Exclusion reasons
    - Non Full-text
    - No orig data
    - No KTA/KTQ addressed
    - No human subjects with ALD
    - Natural Course, < 5 subjects
    - Other
## Technical Expert Panel

### EXPERT PANEL MEMBERS

<table>
<thead>
<tr>
<th>Expert Name</th>
<th>Affiliation</th>
</tr>
</thead>
</table>
| Michele Caggana, Sc.D., FAC | New York State Department of Health  
Director, Newborn Screening Program |
| Ann Moser, BA             | Kennedy Krieger Institute  
Associate Director – Moser Lab |
| Joanne Kurtzberg, MD      | Duke University School of Medicine – Div of Pediatrics  
Director, Carolinas Cord Blood Bank |
| Paul Orchard, MD          | University of Minnesota Medical Center – Pediatric Blood and  
Marrow Transplantation |
| Gerald Raymond, MD        | University of Minnesota Medical Center  
Department of Neurology |
| Florian Eichler, MD       | Massachusetts General Hospital for Children  
Director of Leukodystrophy Center |

### TEP Meetings

- **April 2015**
- **June 2015**
- **July 2015**

### Topics

- Case Definition
- Natural History
- Prevalence, Phenotypes
- Screening & Diagnosis
- Treatment Initiation
- Available Evidence
- Unpublished data
NY NBS Short-term Follow Up Algorithm

Positive Newborn Screen (Tier 1 and Tier 2)

Disease-causing mutation in ABCLD1 identified by sequencing (NBS Tier 3)

No mutation or VUS in ABCLD1 on sequencing performed by NBS
Initial Visit: Order VLCFA and plasmalogen in baby

Male

Newborn: Order VLCFA and send repeat specimen to NBS for C26:0 and confirmatory mutation analysis
Mother: Order VLCFA, send sample to NBS for molecular carrier testing
Female

Newborn: Send repeat specimen to NBS for C26:0 and confirmatory mutation analysis
Both Parents: Send samples to NBS for phasing of molecular findings

Elevated VLCFA, Low plasmalogen

Clinical evaluation consistent with ZSD

Elevated VLCFA, Normal plasmalogen

Clinical evidence of acyl-CoA oxidase deficiency or D-bifunctional protein deficiency

Normal VLCFA and normal plasmalogen

Clinical evidence of peroxisomal disorder

Elevated VLCFA

Normal VLCFA and plasmalogen in newborn, no clinical evidence of peroxisomal disorder

Clinical symptoms of peroxisomal disorder

Cultured fibroblasts, immunohistochemistry or genetic test results consistent with ZSD

VLCFA testing in mother and siblings, deletion analysis of ABCLD1

If deletion/duplication identified, diagnosis confirmed. If deletion analysis negative, Order fibroblasts to confirm absence of ALD

X-linked ALD

Carrier of ALD, Genetic counseling

Possible Peroxisomal Disorder, Continue Evaluation

ZSD

X-linked ALD

Acy-CoA Oxidase Deficiency

D-Bifunctional Protein Deficiency

Peroxisomal Disorder of Unknown Etiology

NY NBS Short-term Follow Up Algorithm

NY State NBS Program – “3-Tier” Screening for X-ALD

<table>
<thead>
<tr>
<th>Tier - Screening Activity</th>
<th>Rate Definition</th>
<th>Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIER 1</td>
<td>MS/MS for C26:0 LPC</td>
<td>Re-test rate (same specimen) = 6,679 of 363,755 newborns = 1.84%</td>
</tr>
<tr>
<td>TIER 2</td>
<td>HPLC &amp; MS/MS for C26:0 LPC</td>
<td>Repeat rate (independent specimen) = 43 borderline retest results, repeats requested of 363,755 newborns tested = 0.0091%</td>
</tr>
<tr>
<td>Mutations analysis – ABCD1 gene</td>
<td>Referral rate = 33 of 363,755 newborns</td>
<td>= 0.0091%</td>
</tr>
</tbody>
</table>

Confirmed Status:
- 14 male ABCD1 mutations (7 with X-ALD dx confirmed)
- 14 female carriers
- 5 Other (secondary, other)
  - 3 ZSD confirmed
  - 1 Aicardi-Goutieres syndrome confirmed

Summary: X-ALD NBS & Short-term Follow up

• The overall prevalence of X-ALD in males and females is about 6 per 100,000 and the prevalence of males with C-CALD is about 1 per 100,000

• There is no genotype-phenotype correlation

• Screening is based on the elevated VLCFA levels

• Screening will also identify most heterozygote females and other peroxisomal disorders

• The NY NBS screening program has a very low rate of positive results, and the positive predictive value if the goal is to detect males with X-ALD is likely 42% (14/33)

• Diagnostic follow-up includes brain MRIs and assessment of adrenal function over time to determine the need for either HSCT or adrenal hormone replacement
Presymptomatic v. Clinical Detection Outcomes

*What are the benefits and harms associated with presymptomatic detection compared to clinical case detection?*
Adrenal Insufficiency

• Untreated adrenal insufficiency can lead to death
• However, no study included in the SER compared treatment outcomes based on the timing of diagnosis of adrenal insufficiency
• One study (Polgreen et al, 2011) describes how diagnosis of adrenal insufficiency can help speed the diagnosis of X-ALD and improve outcomes.
• HSCT does not affect adrenal insufficiency
• Presymptomatic detection of adrenal insufficiency in X-ALD is not a specific focus of the rest of the report
Treatment Outcomes: Child Cerebral X-ALD

- **Disease Status Measures:**
  - **MRI Severity Rating (Loes Score)**
    
    | Loes Score | Clinical Guidelines                          |
    |------------|----------------------------------------------|
    | < 0.5      | Normal, no neurological involvement         |
    | <8 or 9    | Recommendation for HSCT                     |
    | >8 or 9    | Not usually recommended for HSCT            |
  
  - **Neurologic Function Score (NFS)**
  - **ALD-Disability Rating Scale (ALD-DRS)**
Survival, C-CALD untreated (N=283 boys)

5-yr Survival After Symptom Development
66% - survived

10-yr Survival After Symptom Development
43% - survived

Survival, Early stage C-CALD ($NFS \leq 1$, $Loes < 9$): *Transplant* vs. *No Transplant*

5-yr Survival After First Abnormal MRI ($NFS = 0$ or $1$, $Loes < 9$)

- 95% - Transplant ($n=19$)
- 54% - No transplant ($n=30$)
- $p=0.006$

Figure 4: Kaplan-Meier estimates of survival for 19 transplanted patients with early stage cerebral adrenoleukodystrophy and for 30 non-transplanted patients with early stage cerebral adrenoleukodystrophy (i.e., neurological deficit score of 0 or 1 and MRI severity score less than 9). Survival was different in these two groups ($\chi^2=7.47, p=0.006$).

Outcomes, Early vs. Late Stage C-CALD

- At least 5 included outcome studies with N>6 that compare pre-post HCT outcomes between early vs. late stage C-CALD with MRI Severity/Loes scores

<table>
<thead>
<tr>
<th>Pub YR, Author</th>
<th>Title</th>
<th>Journal</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004 Peters et al.</td>
<td>Cerebral X-ALD: the international hematopoietic cell transplantation experience from 1982 to 1999</td>
<td>Blood</td>
<td>94</td>
</tr>
<tr>
<td>2011 Miller et al.</td>
<td>Outcomes after allogeneic HCT for childhood cerebral ALD: the largest single-institution cohort report</td>
<td>Blood</td>
<td>60</td>
</tr>
<tr>
<td>2013 McKinney et al.</td>
<td>Childhood cerebral X-linked ALD: Diffusion tensor imaging measurements for prediction of clinical outcome after HSCT</td>
<td>AJNR</td>
<td>8</td>
</tr>
</tbody>
</table>
### Key Study Variables and Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=94</td>
<td>males X-ALD patients &lt;19 years with complete data (of 126 total patients)</td>
<td></td>
</tr>
<tr>
<td>Med age at HSCT</td>
<td>9.0 y (rg 4.9 – 18.6)</td>
<td></td>
</tr>
<tr>
<td>Detection</td>
<td>N=28 (33%) Family hx N=58 (67%) Symptom onset</td>
<td></td>
</tr>
<tr>
<td>Survival est 5- &amp; 8-yrs (n=94)</td>
<td>56% (95% CI, 44% - 68%)</td>
<td></td>
</tr>
</tbody>
</table>

### Survival est 5-yrs by severity:

| Neurodeficits (ND) >1, Loes ≥9 (n=25) | 45% (95% CI, 23% - 67%) |
| ND ≤1, Loes <9 (n=37) | 92%* (95% CI, 81% -100%) |

(*p<0.01)

**Figure. Survival, C-CALD**

- Solid line=pre-HCT neurodeficits 0, 1 and Loes <9, 92% survival.
- Dashed line=pre-HCT neurodeficits >2, Loes ≥9, 45% survival.

**Single-center BMT Outcomes**

**Key Study Variables and Outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=12, 11 received BMT</td>
<td>X-ALD boys with no HLA matched donors evaluated for BMT. 11 of 12 survived pre-BMT chemo</td>
</tr>
<tr>
<td>Med age at dx</td>
<td>7.0 y</td>
</tr>
<tr>
<td>Med age at HCT</td>
<td>7.41 y</td>
</tr>
<tr>
<td>OS at 6.25 mos (n=11)</td>
<td>66.7%</td>
</tr>
</tbody>
</table>

Does presymptomatic identification lead to improved outcomes for C-CALD compared to usual case detection?

- Case series suggest that there are improved outcomes following HSCT when the Loes score is lower.
- HSCT does not lead to restoration of significant brain involvement.
- However
  - *Is there an ideal threshold for HSCT?*
  - *Studies generally follow time from development of symptoms, without an “anchor” age*
Does presymptomatic identification lead to improved outcomes for C-CALD compared to usual case detection?

• Solution
  – Compare outcomes from cases identified based on the development of clinical symptoms (S) to cases identified through family testing (F)
  – Be “agnostic” to treatment to answer the question about the benefit of knowing that a boy has X-ALD.
  – Restrict to cases of C-CALD

• Two datasets identified
Single Center

- 30 Subjects treated between 2006-2015
  - 17 F
  - 13 S
- Outcome data on 19 subjects
  - 7 F
  - 12 S
- HSCT
  - 3 of the 7 F (1 undergoing eval, 3 “arrested” [“Self-halted”])
  - 7 of the 12 S (4 advanced disease, 1 “arrested”)
Multi-Center

• 59 subjects
  – 25 F
  – 34 S

• All received HSCT
# Treatment Outcomes by Detection: *(Unpublished)*

**Family Risk (F) vs. Symptom onset (S)**

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Single Center (n=19) Detection Group</th>
<th>Multi-Center, Int’l (n=59) Detection Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received HSCT</td>
<td>Family (F) (n=7)</td>
<td>Family-risk (F) (n=25)</td>
</tr>
<tr>
<td></td>
<td>Symptom (S) (n=12)</td>
<td>Symptom (S) (n=34)</td>
</tr>
<tr>
<td>Med Age at HSCT</td>
<td>7 yrs (rg 4-7)</td>
<td>8 yrs (rg 5-9)</td>
</tr>
<tr>
<td></td>
<td>8 yrs (IQR 6-9)</td>
<td>8 yrs (IQR 7-10)</td>
</tr>
<tr>
<td>First avail Loes (med)</td>
<td>0 (IQR 0-1)</td>
<td>4 (IQR 2-5)</td>
</tr>
<tr>
<td></td>
<td>12 (IQR 11-12)</td>
<td>7.5 (IQR 3-11)</td>
</tr>
<tr>
<td>Med Age, First Loes</td>
<td>5 yrs (IQR 4-6)</td>
<td>8 yrs (IQR 5-8)</td>
</tr>
<tr>
<td></td>
<td>7 yrs (IQR 6-9)</td>
<td>8 yrs (IQR 6-9)</td>
</tr>
<tr>
<td>Most Recent Loes (med)</td>
<td>3 (IQR 2-4)</td>
<td>5.75 (IQR 2-11.5)</td>
</tr>
<tr>
<td></td>
<td>12 (IQR 11-20)</td>
<td>13 (IQR 6.5-18)</td>
</tr>
<tr>
<td>Med Age, Recent Loes</td>
<td>10 yrs (rg 8-15)</td>
<td>10.5 yrs (IQR 9-14.5)</td>
</tr>
<tr>
<td></td>
<td>11 yrs (IQR 8-19)</td>
<td>10 yrs (IQR 8-13)</td>
</tr>
</tbody>
</table>
Single Center

Survival, Communicative, and Ambulatory

Survival

Years of Age

Number at risk

Years

F

S

0 5 10 15 20

Survival

0 .25 .5 .75 1

0 7 12 7 12 5 4 2 1 0

95% CI

95% CI

F

S
Multi-Center
Limitations

• Only C-CALD
• Small, select number of subjects with variable follow-up
• Little information on
  – Treatment
  – Disease Course, including functional status
• May not reflect the full spectrum of cases detected through newborn screening
Treatment Summary – Presymptomatic Identification of C-CALD

- No direct evidence about the benefit of presymptomatic identification of adrenal insufficiency
- HSCT improves outcomes, and treatment with a lower Loes score is associated with better outcomes
- Unpublished data suggests that identification through family testing leads to improved survival in late childhood compared to detection after the development of symptoms
Population-Level Outcomes for Newborn Screening of X-ALD

Lisa A. Prosser, Ph.D.
August 27, 2015
Background: Decision analysis

- Validated approach for evidence synthesis
- Using simulation modeling, ranges can be estimated for population-level health benefits
- Explicitly identify assumptions and key areas of uncertainty
Analytic Approach

• Computer simulation model to evaluate outcomes for:
  • Universal newborn screening for X-ALD [NBS]
  • Clinical identification of X-ALD [CI]

• 3 expert panels: April 2015, June 2015, July 2015

• Key health endpoints:
  • # cases identified
  • # deaths averted by 15 years of age
Model Schematic: NBS Submodel

Newborn Screening

- Abnormal Screen (1st and 2nd tier)
  - Confirmatory Testing
    - X-ALD (ABCD1 Mutation)
      - Childhood/Adolescent Cerebral ALD
        - Survive
        - Die
    - ALD-Heterozygote ABCD1 (female carriers)
      - Adrenal Insufficiency Only
    - Peroxisomal/Other Disorders
      - Asymptomatic
    - No evidence of disease
      - Adult Onset Forms (AMN & Adult CALD)
      - Remain Asymptomatic
- False Positive
- True Negative
- False Negative

Newborns

Clinical Identification

1Not at high risk
2With or without adrenal insufficiency
Model Schematic: CI Submodel

Newborn Screening → See previous page

Newborns

- Clinical Identification
  - X-ALD
  - Female Carriers
  - Normal

Childhood/Adolescent Cerebral ALD
  - Survive
  - Die

Adrenal Insufficiency Only

Adult Onset (AMN & Adult CALD)

1 Not at high risk
2 With or without adrenal insufficiency
3 Can also include peroxisomal/other disorders
Modeling Assumptions

- Screening projections based on NY data
- Other model inputs derived from evidence review, expert panel, assumptions
- Potential benefits of earlier treatment are uncertain but may include:
  - Improved survival
  - Improved cognitive outcomes (not modeled, except for NANC state)
# Results: Annual Cases of X-ALD identified

<table>
<thead>
<tr>
<th></th>
<th>NBS</th>
<th>Clinical Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCALD</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>46 (32-68)</td>
<td>46 (32-66)</td>
</tr>
<tr>
<td>Adrenal Insufficiency Only</td>
<td>12 (8-18)</td>
<td>12 (8-17)</td>
</tr>
<tr>
<td>Adult Onset</td>
<td>85 (24-125)</td>
<td>34 (24-49)</td>
</tr>
<tr>
<td><strong>Total X-ALD</strong></td>
<td>143 (64-211)</td>
<td>92 (64-132)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Assuming healthy annual newborn cohort of 4 million, not at higher risk of X-ALD

<sup>2</sup>With or without adrenal insufficiency
## Results: Survival Outcomes at 15 years of age\(^1\)

### Table 15.a. Projected survival without NANC\(^2\)

<table>
<thead>
<tr>
<th>Survival without NANC (# cases)</th>
<th>Deaths or cases of NANC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screened/Treated if Indicated</strong></td>
<td></td>
</tr>
<tr>
<td>Most Likely</td>
<td>46</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(5, 68)</td>
</tr>
<tr>
<td>clinically diagnosed/Treated if Indicated</td>
<td>9</td>
</tr>
<tr>
<td>Most Likely</td>
<td>37</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(17, 64)</td>
</tr>
</tbody>
</table>

### Table 15. b. Projected survival, treated patients only\(^3\)

<table>
<thead>
<tr>
<th>Survival (# Cases)</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screened/Received Transplant</strong></td>
<td></td>
</tr>
<tr>
<td>Most Likely</td>
<td>46</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(22, 68)</td>
</tr>
<tr>
<td>clinically diagnosed/Received Transplant</td>
<td></td>
</tr>
<tr>
<td>Most Likely</td>
<td>28</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(11, 52)</td>
</tr>
</tbody>
</table>

---

\(^{1}\)95% CIs derived assuming a binomial distribution; \(^{2}\)NANC = Non-ambulatory, non-communicative state; unpublished data from Eichler et al, 2015; \(^{3}\)Unpublished data from multisite study.
Summary

- Projected health benefits for newborn screening compared with clinical identification for cases of X-ALD by 15 years:
  - 18 deaths averted (range: 7-44), or
  - 37 cases of death or NANC averted (range: 17-64)

- Base case projections assume equal numbers of childhood/adolescent CALD identified under each alternative.
  - However, newborn screening may result in a higher incidence of X-ALD attributable to missed cases, and/or spectrum bias.
  - Under certain scenarios, the additional number of adult cases of AMN identified is projected to be as high as 76 cases annually.
Public Health System Impact Assessment

X-linked Adrenoleukodystrophy
Overview

- Background
- APHL’s Role
- Methods
- Results
- Summary
PHSI Background

• Recommendations are based on
  – Certainty of net benefit
  – Feasibility and readiness of implementing comprehensive screening
Definition of Readiness

• Ready
  – most NBS programs could implement within 1 year

• Developmental Readiness
  – most NBS programs could implement within 1–3 years

• Unprepared
  – most NBS programs would take more than 3 years to implement
Components of Feasibility

- An established and available screening test
- A clear approach to diagnostic confirmation
- Acceptable treatment plan, and
- Established approach to long-term follow-up plans
Why is this Assessment Important?

• Opportunity to
  – Understand the “real world” barriers and facilitators related to screening
  – Evaluate opportunity costs
Methods

• X-ALD factsheet
• Webinar and outreach
• Survey to 53 U.S. states and territories
• Informant interviews with 4 state NBS programs that are or are planning X-ALD newborn screening
## Results: Interviews

<table>
<thead>
<tr>
<th></th>
<th>Legislative Mandate</th>
<th>Statewide Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>California</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Connecticut</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>New Jersey</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Results: Interviews

Challenges from NBS program screening:

- Validating the X-ALD assay
- Determining how to multiplex the assay with LSDs to get consistent results
- Adjusting the screening cutoff to capture as many cases as possible
- Resolving follow up issues related to identifying asymptomatic males and secondary targets (e.g., female carriers and females with peroxisomal disorders)
Results: Interviews

Factors aiding implementation from NBS program screening:

- Consistent communication/developing relationships with specialty centers, health care providers, and diagnostic centers
- Not needing to procure new equipment
- Having existing resources for screening
## Results: States with Mandates

<table>
<thead>
<tr>
<th>State</th>
<th>Year Mandate Received</th>
<th>Screening REQUIRED immediately once added to RUSP</th>
<th>Conditions to be met before screening begins</th>
<th>Timeframe to fulfill conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>2014</td>
<td>Yes</td>
<td>None</td>
<td>Not specified</td>
</tr>
</tbody>
</table>
| CT    | 2013                  | No                                              | • Development and validation of method or FDA approved kit  
• Availability of necessary reagents for tests | Not specified                   |
| NJ    | 2013                  | No                                              | • Development of a reliable test  
• Availability of quality assurance materials  
• Inclusion on the RUSP  
• Review by the Department of Health  
• Acquisition of equipment | Six months after condition is added to RUSP |
Results: Interviews

Challenges from states with mandate to screen:

- Realistic time frame
- Working with neurologists for first time
- Referral process
- Duration to track patients
- Follow-up issues
- Ensuring availability of specimens for validation
- Hiring challenges
Results: Interviews

Factors that have/will aid in implementation:

- Communicating and sharing information with other NBS programs
- Attending national trainings
- Adequate clinical and follow-up data
- Addition of other disorders on the RUSP
- Insight from NBS programs screening
- Adequate time to implement
Results: Survey

• Response rate of 70%
  – 27 responses from state NBS programs
  – 6 responses from programs that contract commercially or regionally

• Four states NBS programs were excluded from the analysis because they participated in the interview
# Results: Duration for Authorization

<table>
<thead>
<tr>
<th>Answer</th>
<th>Number of Programs</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>5</td>
<td>15%</td>
</tr>
<tr>
<td>1 to 3 years</td>
<td>20</td>
<td>61%</td>
</tr>
<tr>
<td>More than 3 years</td>
<td>8</td>
<td>24%</td>
</tr>
<tr>
<td>Never</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
## Results: Implementation Challenges

<table>
<thead>
<tr>
<th>Answer</th>
<th>Number of Programs</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide screening test</td>
<td>20</td>
<td>61%</td>
</tr>
<tr>
<td>Short-term follow-up of abnormals</td>
<td>20</td>
<td>61%</td>
</tr>
<tr>
<td>Increase of NBS fee</td>
<td>16</td>
<td>49%</td>
</tr>
<tr>
<td>Long-term follow up for carriers and individuals with peroxisomal disorders</td>
<td>15</td>
<td>46%</td>
</tr>
<tr>
<td>Support to ALD specialists</td>
<td>12</td>
<td>36%</td>
</tr>
<tr>
<td>Treatment support for ALD</td>
<td>8</td>
<td>24%</td>
</tr>
<tr>
<td>Other—please specify</td>
<td>3</td>
<td>9%</td>
</tr>
</tbody>
</table>
### Results: Implementation Resources

<table>
<thead>
<tr>
<th>Resource</th>
<th>Have Already</th>
<th>Do not have BUT can get within one year</th>
<th>Cannot get within one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to appropriate diagnostic services after a positive screen (e.g., diagnostic testing, clinical evaluations) for…</td>
<td>46%</td>
<td>21%</td>
<td>33%</td>
</tr>
<tr>
<td>Treatment centers for expected ALD case load (n=33)</td>
<td>36%</td>
<td>15%</td>
<td>49%</td>
</tr>
<tr>
<td>Specialists to cover expected ALD case load (n=33)</td>
<td>33%</td>
<td>21%</td>
<td>46%</td>
</tr>
<tr>
<td>Sufficient number of NBS staff to notify and track ALD NBS results (n=33)</td>
<td>24%</td>
<td>39%</td>
<td>36%</td>
</tr>
<tr>
<td>Follow up protocols for ALD cases, carriers, and individuals with peroxisomal disorders (n=33)</td>
<td>70%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Laboratory technical expertise to screen for ALD (n=29)</td>
<td>31%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>LIMS capacity and instrumentation interface for ALD (n=29)</td>
<td>10%</td>
<td>52%</td>
<td>38%</td>
</tr>
<tr>
<td>Sufficient number of technical staff to screen for ALD (n=29)</td>
<td>3%</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>Quantity and type of laboratory equipment for ALD (n=29)</td>
<td>3%</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>Onsite genotyping as part of a third-tier test for ALD (n=29)</td>
<td>35%</td>
<td></td>
<td>66%</td>
</tr>
<tr>
<td>Screening approach for ALD (MS/MS and HPLC) (n=27)</td>
<td>4%</td>
<td>56%</td>
<td>41%</td>
</tr>
<tr>
<td>Availability of the screening test in your contracted laboratory (n=6)</td>
<td>17%</td>
<td></td>
<td>83%</td>
</tr>
</tbody>
</table>
## Results: Implementation Resources

<table>
<thead>
<tr>
<th>Issue</th>
<th>Major Barrier</th>
<th>Minor Barrier</th>
<th>No Impact</th>
<th>Minor Facilitator</th>
<th>Major Facilitator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per specimen to conduct ALD screening (personnel, equipment, reagents) (n=33)</td>
<td>19 (58%)</td>
<td>13 (39%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements) (n=33)</td>
<td>16 (49%)</td>
<td>17 (52%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cost of treatment for newborns diagnosed with ALD (n=33)</td>
<td>9 (27%)</td>
<td>11 (33%)</td>
<td>13 (39%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other non-NBS public health priorities within your state (n=33)</td>
<td>9 (27%)</td>
<td>12 (36%)</td>
<td>12 (36%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Expected clinical outcomes of newborns identified with ALD from screening (n=33)</td>
<td>8 (24%)</td>
<td>4 (12%)</td>
<td>8 (24%)</td>
<td>7 (21%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>Expected cost-benefit of screening for ALD in your state (n=33)</td>
<td>6 (18%)</td>
<td>6 (18%)</td>
<td>11 (33%)</td>
<td>7 (21%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Advocacy for screening for ALD (n=33)</td>
<td>2 (6%)</td>
<td>2 (6%)</td>
<td>11 (33%)</td>
<td>14 (42%)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Extent to which the screening test for ALD can be multiplexed with other disorders (n=29)*</td>
<td>6 (21%)</td>
<td>9 (31%)</td>
<td>3 (10%)</td>
<td>4 (14%)</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Predicted run time to screen for ALD as it relates to other workload (n=29)*</td>
<td>4 (14%)</td>
<td>14 (48%)</td>
<td>9 (31%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Results: Most Significant Barrier

• 15 NBS programs cited funding/costs as the most significant barrier

• Other barriers:
  ➢ Legislative approval or not having the condition on the RUSP
  ➢ Staffing/hiring
  ➢ Waiting for contract laboratory to get the screening test
  ➢ Competing public health priorities
Results: Greatest Facilitator

• Eight NBS programs cited the potential of multiplexing with other disorders as being the most significant facilitator

• Other facilitators:
  - Addition to the RUSP
  - Benefits of early detection
  - Readiness of contract laboratory/other program that can perform testing
  - Advocacy
# Duration for Implementation

<table>
<thead>
<tr>
<th>Activity</th>
<th>&lt;1 year</th>
<th>1 to 3 years</th>
<th>More than 3 years</th>
<th>Activity is not required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop follow-up protocols for ALD (n=33)</td>
<td>55%</td>
<td>33%</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Consult with medical staff and specialists to add test for ALD (n=33)</td>
<td>6%</td>
<td>52%</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>Hire necessary laboratory and/or follow-up staff for ALD (n=33)</td>
<td>39%</td>
<td>39%</td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td>Pilot test the ALD screening process within your state, after validation has taken place (n=29)</td>
<td>35%</td>
<td>41%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Obtain and procure equipment for ALD screening (n=29)</td>
<td>31%</td>
<td>52%</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Select, develop, and validate the ALD screening test within your laboratory assuming you are NOT multiplexing with other...</td>
<td>28%</td>
<td>52%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>Select, develop, and validate the ALD screening test within your laboratory assuming you are multiplexing with other...</td>
<td>28%</td>
<td>52%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Entire process from obtaining equipment to full reporting and implementing statewide ALD screening (assuming that...</td>
<td>7%</td>
<td>66%</td>
<td>24%</td>
<td>3%</td>
</tr>
<tr>
<td>Add the ALD screening test to the existing outside laboratory contract (n=6)</td>
<td>17%</td>
<td>50%</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>
Strengths of PHSI

- Survey response rate of 70%
- Webinar and factsheet for survey responders
- Survey assessed perceptions about implementation based on experiences with other disorders
- Interviews assessed real world experiences
Limitations of PHSI

- Assumption that approval had occurred and funds were allocated
- Hypothetical survey questions and subjective responses
- Limited data on screening for X-ALD in NBS setting
Conclusions: Readiness

- Most (61%) of the state NBS programs that were surveyed and 2 out of 3 states with mandates reported that it would take between 1 and 3 years to implement screening for X-ALD after approval and allocation of funds.
- Developmentally ready at best.
Conclusions: Feasibility

• Establishing long-term follow up plans remains difficult
• Several follow-up issues were noted:
  ➢ Uncertainty regarding age of onset (often later than most NBS disorders)
  ➢ Length of time to track patients
  ➢ Timing of the development of CALD or adrenal insufficiency
  ➢ Referral process
Summary

• Costs associated with screening and competing public health interests continue to hinder implementation of other recommended conditions

• States with mandates do not have funds for sustained screening

• The NBS program that has begun screening provides important lessons
Overall Summary

• X-ALD is associated with significant morbidity and mortality in affected males
• HSCT can be an effective therapy for those with C-CALD
  – Studies support that outcomes are improved when there is less cerebral involvement
  – Unpublished data suggest that there is decreased morbidity/mortality in late childhood among individuals who are diagnosed through family testing compared to after the development of symptoms
• Adrenal insufficiency is common and can be treated with replacement therapy
  – No data about the benefit of early identification compared to usual case detection
• Harms
  – Screening identifies boys with C-CALD but also identifies heterozygote females and other peroxisomal disorders
  – Individuals identified through screening may need many years of follow-up with uncertain course of disease
  – Shifting transplant earlier exposes the risk of transplant to an earlier age
• Most states anticipate needing at least 1-3 years to adopt screening once funding becomes available
Thank You!

Questions?

Presentation Contact:
Alex R. Kemper, MD, MPH, MS
alex.kemper@duke.edu